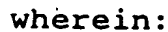


1. A method for modulating process(es) mediated by retinoid receptors, said method comprising conducting said process(es) in the presence of at least one compound of the structure:



any two or more of the R groups can be linked to one another to form one or more ring structures.

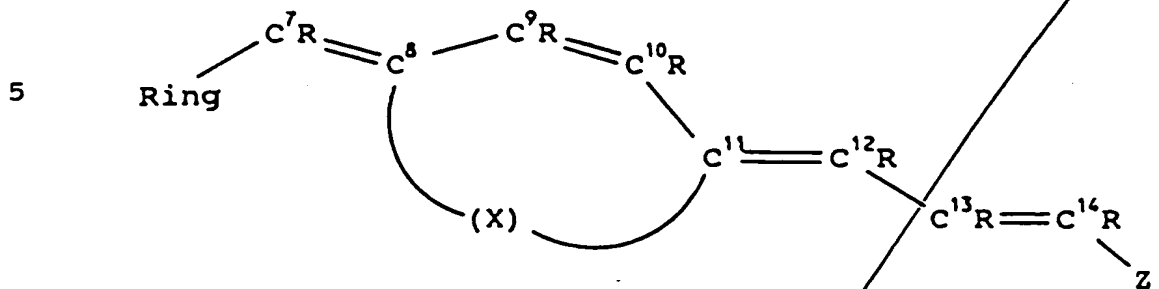
2. A method according to claim 1 wherein said retinoid receptor is selected from retinoic acid receptor-alpha, retinoic acid receptor-beta, or retinoic acid receptor-gamma.

3. A method according to claim 1 wherein said retinoid receptor is selected from retinoid X receptor-alpha, retinoid X receptor-beta, or retinoid X receptor-gamma.

4. A method according to claim 1 wherein said process is selected from in vitro cellular differentiation, in vitro cellular proliferation, in vitro proliferation of melanoma cell lines, in vitro  
5 differentiation of mouse teratocarcinoma cells (F9 cells), in vitro differentiation of human epidermal keratinocytes, regulation of cellular retinol binding protein (CRBP), or in vitro limb morphogenesis.

5. A method according to claim 1 wherein said process is selected from the in vivo modulation of lipid metabolism, in vivo modulation of skin-related processes, or in vivo modulation of malignant cell  
5 development.

6. A method according to claim 1 wherein said compound has the structure (I):



10

Structure I

wherein:

15

X is  $-(\text{CR}_2)_x-\text{X}'-(\text{CR}_2)_y-$ ,

X' is selected from -O-, carbonyl, -S-,  
-S(O)-, -S(O)<sub>2</sub>-, thiocarbonyl, -NR"-, or -CR<sub>2</sub>-,

"Ring" is a cyclic moiety;

20

Z is selected from carboxyl, carboxaldehyde, hydroxyalkyl, thioalkyl, hydroxyalkyl phosphate, alkyl ether of a hydroxyalkyl group, alkyl thioether of a thioalkyl group, esters of hydroxyalkyl groups, thioesters of hydroxyalkyl group, esters of thioalkyl groups, thioesters of thioalkyl groups, aminoalkyl, N-acyl aminoalkyl, or carbamate; and

25

each R is independently selected from H, halogen, alkyl, aryl, hydroxy, thiol, alkoxy, thioalkoxy, or amino;

R" is hydrogen, alkyl, hydroxy, thiol, or alkoxy acyl;

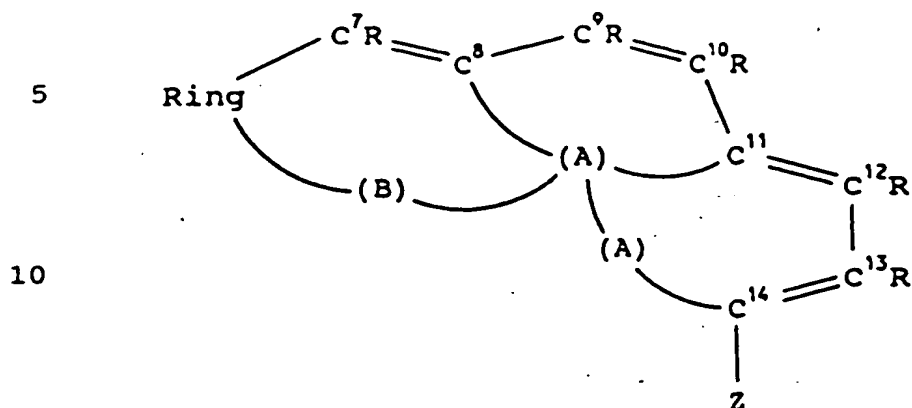
30

x is 0, 1 or 2,

y is 0, 1, or 2, and

$x + y \leq 2$ .

9. A method according to claim 1 wherein said compound has the structure (IV):

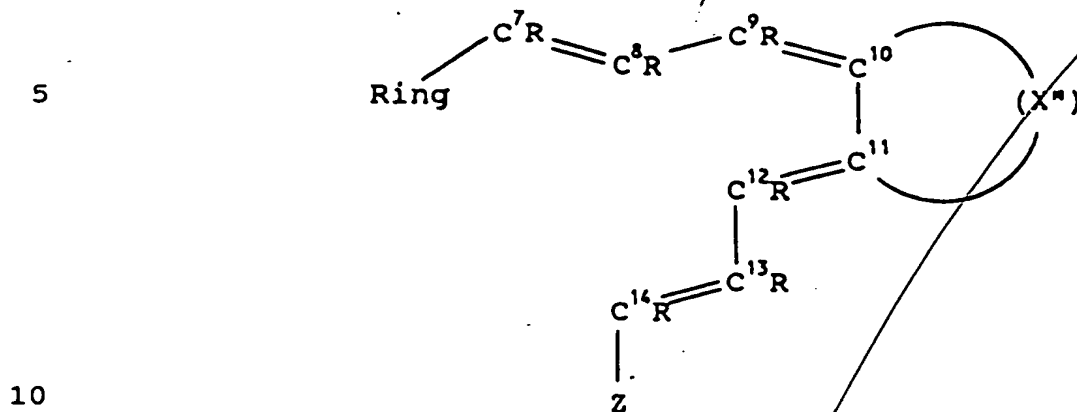


Structure IV

wherein:

- 15                      one A is X and the other A is X',  
                     B is X',  
                     X is  $-(\text{CR}_2)_x\text{-X}'-(\text{CR}_2)_y\text{-}$ ,  
                     X' is selected from -O-, carbonyl, -S-,  
                     -S(O)-, -S(O)<sub>2</sub>-, thiocarbonyl, -NR"-, or -CR<sub>2</sub>-,  
 20                      "Ring" is a cyclic moiety;  
                     Z is selected from carboxyl, carboxaldehyde,  
                     hydroxyalkyl, thioalkyl, hydroxyalkyl phosphate,  
                     alkyl ether of a hydroxyalkyl group, alkyl  
                     thioether of a thioalkyl group, esters of  
 25                      hydroxyalkyl groups, thioesters of hydroxyalkyl  
                     group, esters of thioalkyl groups, thioesters of  
                     thioalkyl groups, aminoalkyl, N-acyl aminoalkyl,  
                     or carbamate; and  
                     each R is independently selected from H,  
 30                      halogen, alkyl, aryl, hydroxy, thiol, alkoxy,  
                     thioalkoxy, amino, or any of the Z substituents;  
                     R' is hydrogen, alkyl, hydroxy, thiol, or  
                     alkoxy acyl;  
                     x is 0, 1 or 2,  
 35                      y is 0, 1, or 2, and  
                     x + y ≤ 2.

10. A method according to claim 1 wherein said compound has the structure (V):



Structure V

wherein:

X'' is  $-[(CR_2)_a-X']-(CR_2)_b-$ ,

X' is selected from -O-, carbonyl, -S-,  
15 -S(O)-, -S(O)<sub>2</sub>-, thiocarbonyl, -NR'', or -CR<sub>2</sub>-,

"Ring" is a cyclic moiety;

Z is selected from carboxyl, carboxaldehyde,  
hydroxyalkyl, thioalkyl, hydroxyalkyl phosphate,  
alkyl ether of a hydroxyalkyl group, alkyl  
20 thioether of a thioalkyl group, esters of  
hydroxyalkyl groups, thioesters of hydroxyalkyl  
group, esters of thioalkyl groups, thioesters of  
thioalkyl groups, aminoalkyl, N-acyl aminoalkyl,  
or carbamate; and

25 each R is independently selected from H,  
halogen, alkyl, aryl, hydroxy, thiol, alkoxy,  
thioalkoxy, amino, or any of the Z substituents;

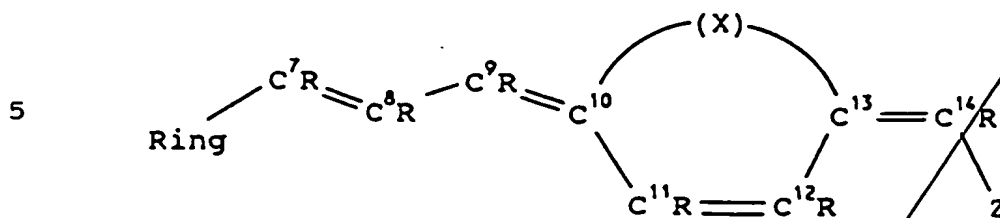
R'' is hydrogen, halogen, alkyl, hydroxy, or  
thiol;

30 a is 0, 1, 2, 3 or 4,

b is 0, 1, 2, 3, or 4, and

a + b is  $\geq 2$ , but  $\leq 4$ .

7. A method according to claim 1 wherein said compound has the structure (II):



10 Structure II

wherein:

X is  $-[(CR_2)_x-X'-(CR_2)_y]-$ ,

X' is selected from -O-, carbonyl, -S-,  
-S(O)-, -S(O)<sub>2</sub>-, thiocarbonyl, -NR"-, or -CR<sub>2</sub>-,

"Ring" is a cyclic moiety;

15 Z is selected from carboxyl, carboxaldehyde, hydroxyalkyl, thioalkyl, hydroxyalkyl phosphate, alkyl ether of a hydroxyalkyl group, alkyl thioether of a thioalkyl group, esters of hydroxyalkyl groups, thioesters of hydroxyalkyl group, esters of thioalkyl groups, thioesters of thioalkyl groups, aminoalkyl, N-acyl aminoalkyl, or carbamate; and

25 each R is independently selected from H, halogen, alkyl, aryl, hydroxy, thiol, alkoxy, thioalkoxy, amino, or any of the Z substituents;

R" is hydrogen, alkyl, hydroxy, thiol, or alkoxy acyl;

x is 0, 1 or 2,

y is 0, 1, or 2, and

30 x + y ≤ 2.

5



wherein:

15

X is  $-[(CR_2)_x - X' - (CR_2)_y] -$ ,

X' is selected from -O-, carbonyl, -S-,

-S(O)-, -S(O)<sub>2</sub>-, thiocarbonyl, -NR"-, or -CR<sub>2</sub>-,

"Ring" is a cyclic moiety;

20

Z is selected from carboxyl, carboxaldehyde, hydroxyalkyl, thioalkyl, hydroxyalkyl phosphate, alkyl ether of a hydroxyalkyl group, alkyl thioether of a thioalkyl group, esters of hydroxyalkyl groups, thioesters of hydroxyalkyl group, esters of thioalkyl groups, thioesters of thioalkyl groups, aminoalkyl, N-acyl aminoalkyl, or carbamate; and

**25.**

each R is independently selected from H, halogen, alkyl, aryl, hydroxy, thiol, alkoxy, thioalkoxy, amino, or any of the Z substituents;

30

/R" is hydrogen, alkyl, hydroxy, thiol, or alkoxy acyl;

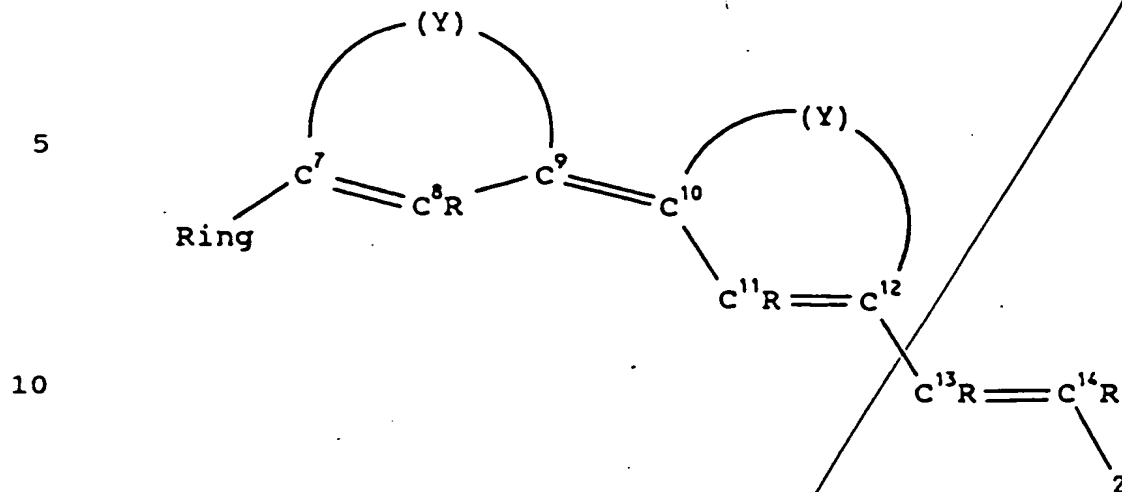
**x is 0, 1 or 2,**

y is 0, 1, or 2, and

35

$$x + y \leq 2.$$

11. A method according to claim 1 wherein said compound has the structure (VI):



Structure VI

wherein:

15

Y is  $-(\text{CR}_2)_c-\text{X}'-(\text{CR}_2)_d-$ ,

X' is selected from -O-, carbonyl, -S-,  
-S(O)-, -S(O)<sub>2</sub>-, thiocarbonyl, -NR"-, or -CR<sub>2</sub>-,  
"Ring" is a cyclic moiety;

20

Z is selected from carboxyl, carboxaldehyde,  
hydroxyalkyl, thioalkyl, hydroxyalkyl phosphate,  
alkyl ether of a hydroxyalkyl group, alkyl  
thioether of a thioalkyl group, esters of  
hydroxyalkyl groups, thioesters of hydroxyalkyl  
group, esters of thioalkyl groups, thioesters of  
thioalkyl groups, aminoalkyl, N-acyl aminoalkyl,  
or carbamate; and

25

each R is independently selected from H,  
halogen, alkyl, aryl, hydroxy, thiol, alkoxy,  
thioalkoxy, amino, or any of the Z substituents;

30

R" is hydrogen, alkyl, hydroxy, thiol, or  
alkoxy acyl;

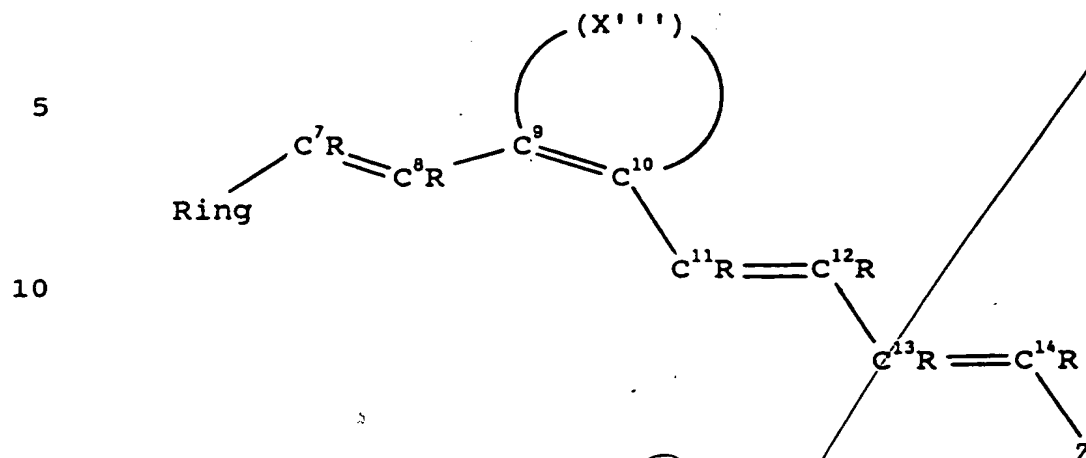
c is 0, 1, 2 or 3,

d is 0, 1, 2 or 3, and

c + d ≥ 1, but ≤ 3.



12. A method according to claim 1 wherein said compound has the structure (VII):



Structure VII

wherein:

15 X''' is X'' or an unsaturated linking group having the structure:

$-[Q = CR - J]-$ ,

wherein Q is  $-N=$  or  $-CR=$ , and J is  $-CR=CR-$ ,  $-N=CR-$ ,  $-CR=N-$ ,  $-O-$ ,  $-S-$ , or  $-NR''-$ ,

20 thereby incorporating  $C^9$  and  $C^{10}$  of the rexoid compound into an aromatic (or pseudo-aromatic) ring,

X'' is  $-[(CR_2)_a-X'-(CR_2)_b]-$ ,

25 X' is selected from  $-O-$ , carbonyl,  $-S-$ ,  $-S(O)-$ ,  $-S(O)_2-$ , thiocarbonyl,  $-NR''-$ , or  $-CR_2-$ ,

"Ring" is a cyclic moiety;

30 Z is selected from carboxyl, carboxaldehyde, hydroxyalkyl, thioalkyl, hydroxyalkyl phosphate, alkyl ether of a hydroxyalkyl group, alkyl thioether of a thioalkyl group, esters of hydroxyalkyl groups, thioesters of hydroxyalkyl group, esters of thioalkyl groups, thioesters of thioalkyl groups, aminoalkyl, N-acyl aminoalkyl, or carbamate; and

35

each R is independently selected from H, halogen, alkyl, aryl, hydroxy, thiol, alkoxy, thioalkoxy, amino, or any of the Z substituents;

R" is hydrogen, alkyl, hydroxy, thiol, or alkoxy acyl;

40

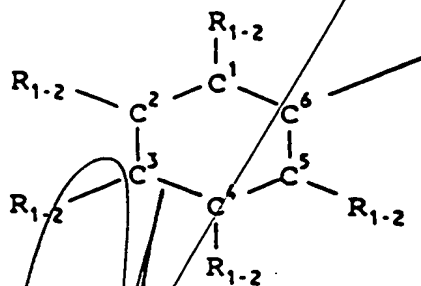
a is 0, 1, 2, 3 or 4,

b is 0, 1, 2, 3, or 4, and

a + b is  $\geq 2$ , but  $\leq 4$ .

13. A method according to claim 1 wherein Ring has the following structure:

5



10 wherein:

each R is independently selected from H, halogen, alkyl, aryl, hydroxy, thiol, alkoxy, thioalkoxy, amino, or any of the Z substituents;

15

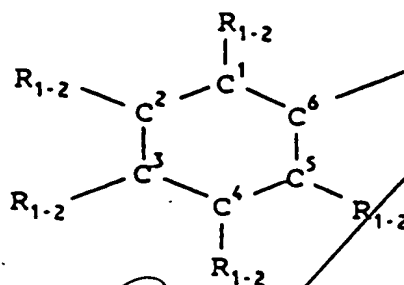
any one of C<sup>2</sup>, C<sup>3</sup>, or C<sup>4</sup> can be replaced with -O-, carbonyl (>CO), -S-, -S(O)-, -S(O)<sub>2</sub>-, thiocarbonyl (>CS), or -NR"-;

R" is hydrogen, alkyl, hydroxy, thiol, or alkoxy acyl; and

20

said cyclic moiety exists as the saturated, 2-ene, 3-ene, 4-ene, or 5-ene mono-unsaturated isomer, or the 2,4-, 2,5-, or 3,5-diene derivative thereof; or an aromatic derivative thereof.

14. A method according to claim 6 wherein Ring has the following structure:



10 wherein:

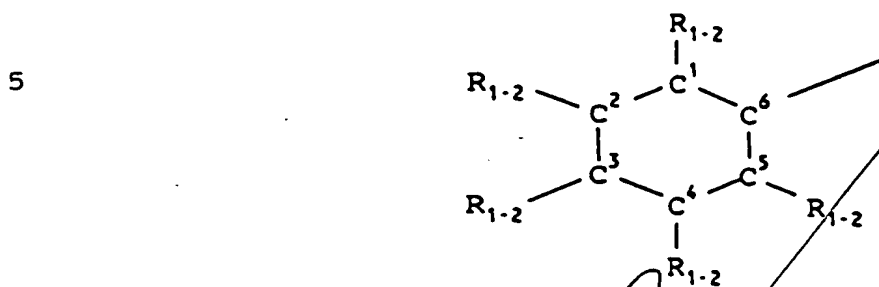
each R is independently selected from H, halogen, alkyl, aryl, hydroxy, thiol, alkoxy, thioalkoxy, amino, or any of the Z substituents;

15 any one of C<sup>2</sup>, C<sup>3</sup>, or C<sup>4</sup> can be replaced with -O-, carbonyl (>CO), -S-, -S(O)-, -S(O)<sub>2</sub>-, thiocarbonyl (>CS), or -NR"-;

R" is hydrogen, alkyl, hydroxy, thiol, or alkoxy acyl; and

20 said cyclic moiety exists as the saturated, 2-ene, 3-ene, 4-ene, or 5-ene mono-unsaturated isomer, or the 2,4-, 2,5-, or 3,5-diene derivative thereof, or an aromatic derivative thereof.

15. A method according to claim 7 wherein Ring has the following structure:



10 wherein:

each R is independently selected from H, halogen, alkyl, aryl, hydroxy, thiol, alkoxy, thioalkoxy, amino, or any of the Z substituents;

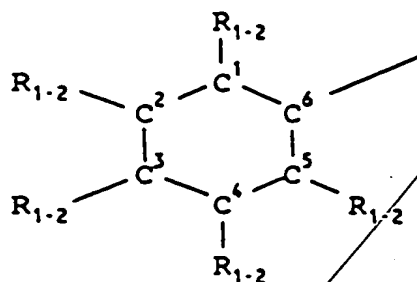
15 any one of C<sup>2</sup>, C<sup>3</sup>, or C<sup>4</sup> can be replaced with -O-, carbonyl (>CO), -S-, -S(O)-, -S(O)<sub>2</sub>-, thiocarbonyl (>CS), or -NR"-;

R" is hydrogen, alkyl, hydroxy, thiol, or alkoxy acyl; and

20 said cyclic moiety exists as the saturated, 2-ene, 3-ene, 4-ene, or 5-ene mono-unsaturated isomer, or the 2,4-, 2,5-, or 3,5-diene derivative thereof.

16. A method according to claim 8 wherein Ring has the following structure:

5



10 wherein:

each R is independently selected from H, halogen, alkyl, aryl, hydroxy, thiol, alkoxy, thioalkoxy, amino, or any of the Z substituents;

15

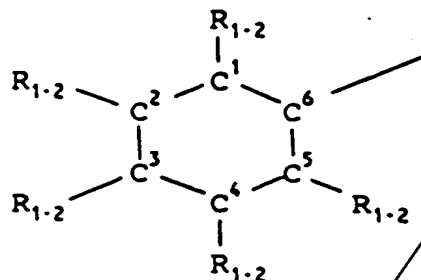
any one of C<sup>2</sup>, C<sup>3</sup>, or C<sup>4</sup> can be replaced with -O-, carbonyl (>CO), -S-, -S(O)-, -S(O)<sub>2</sub>-, thiocarbonyl (>CS), or -NR"-;

R" is hydrogen, alkyl, hydroxy, thiol, or alkoxy acyl; and

20

said cyclic moiety exists as the saturated, 2-ene, 3-ene, 4-ene, or 5-ene mono-unsaturated isomer, or the 2,4-, 2,5-, or 3,5-diene derivative thereof; or an aromatic derivative thereof.

17. A method according to claim 9 wherein Ring has the following structure:



10 wherein:

each R is independently selected from H, halogen, alkyl, aryl, hydroxy, thiol, alkoxy, thioalkoxy, amino, or any of the Z substituents;

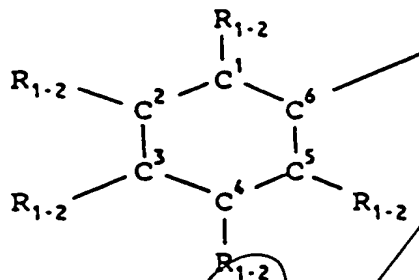
15 any one of C<sup>2</sup>, C<sup>3</sup>, or C<sup>4</sup> can be replaced with -O-, carbonyl (>CO), -S-, -S(O)-, -S(O)<sub>2</sub>-, thiocarbonyl (>CS), or -NR"-;

R" is hydrogen, alkyl, hydroxy, thiol, or alkoxy acyl; and

20 said cyclic moiety exists as the saturated, 2-ene, 3-ene, 4-ene, or 5-ene mono-unsaturated isomer, or the 2,4-, 2,5-, or 3,5-diene derivative thereof; or an aromatic derivative thereof.

18. A method according to claim 10 wherein  
Ring has the following structure:

5



10 wherein:

15

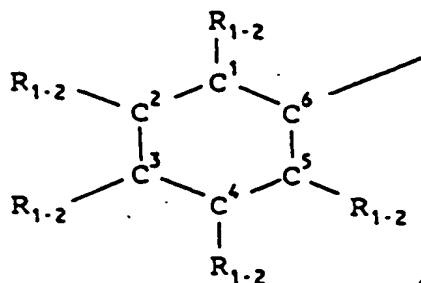
each R is independently selected from H,  
halogen, alkyl, aryl, hydroxy, thiol, alkoxy,  
thioalkoxy, amino, or any of the Z substituents;  
any one of C<sup>1</sup>, C<sup>3</sup>, or C<sup>4</sup> can be replaced with  
-O-, carbonyl (>CO), -S-, -S(O)-, -S(O)<sub>2</sub>-,  
thiocarbonyl (>CS), or -NR"-;

R" is hydrogen, alkyl, hydroxy, thiol, or  
alkoxy acyl; and

20

said cyclic moiety exists as the saturated,  
2-ene, 3-ene, 4-ene, or 5-ene mono-unsaturated  
isomer, or the 2,4-, 2,5-, or 3,5-diene  
derivative thereof; or an aromatic derivative  
thereof.

19. A method according to claim 11 wherein Ring has the following structure:



10 wherein:

each R is independently selected from H, halogen, alkyl, aryl, hydroxy, thiol, alkoxy, thioalkoxy, amino, or any of the Z substituents;

15 any one of C<sup>2</sup>, C<sup>3</sup>, or C<sup>4</sup> can be replaced with -O-, carbonyl (>CO), -S-, -S(O)-, -S(O)<sub>2</sub>-, thiocarbonyl (>CS), or -NR"-;

R" is hydrogen, alkyl, hydroxy, thiol, or alkoxy acyl; and

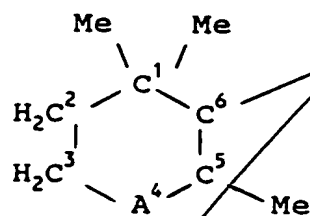
20 said cyclic moiety exists as the saturated, 2-ene, 3-ene, 4-ene, or 5-ene mono-unsaturated isomer, or the 2,4-, 2,5-, or 3,5-diene derivative thereof; or an aromatic derivative thereof.

20. A method according to claim 1 wherein said compound is selected from 9-cis-retinoic acid, 9-phenyl-9-cis-retinoic acid, 4-hydroxy-9-cis-retinoic acid, 4-keto-9-cis-retinoic acid, 9,11-dicis retinoic acid, 5 and 9-cis-locked derivatives of retinoic acid selected from Structures I-VII as set forth in the specification, wherein Z is carboxyl and Ring is a  $\beta$ -ionone or  $\beta$ -ionone-like species having the structure:



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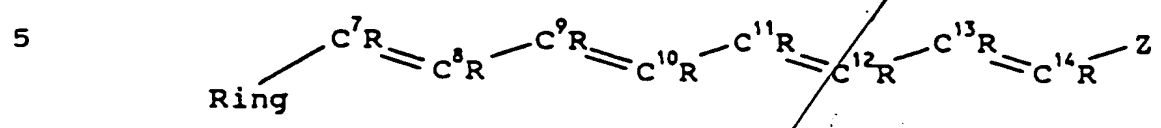


15 wherein A<sup>4</sup> is selected from >CH<sub>2</sub>, >C=O or >C-OH.

21. A method according to claim 1 wherein Ring has four or five carbon atoms and is selected from cyclopentane, cyclopentene, dihydropyran, tetrahydropyran, piperidine, dihydrothiopyran, tetrahydrothiopyran, dihydrofuran, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, or derivatives thereof.

22. A method to modulate processes mediated by retinoid receptors, said method comprising conducting said process in the presence of:

(a) at least one compound of the structure:



wherein:

10 each site of unsaturation in the side chain comprising carbon atoms C<sup>7</sup> through C<sup>14</sup> has a trans configuration;

"Ring" is a cyclic moiety;

15 Z is selected from carboxyl, carboxaldehyde, hydroxyalkyl, thioalkyl, hydroxyalkyl phosphate, alkyl ether of a hydroxyalkyl group, alkyl thioether of a thioalkyl group, esters of hydroxyalkyl groups, thioesters of hydroxyalkyl group, esters of thioalkyl groups, thioesters of thioalkyl groups, aminoalkyl, N-acyl aminoalkyl, carbamate, and the like; and

20 each R is independently selected from H, halogen, alkyl, aryl, hydroxy, thiol, alkoxy, thioalkoxy, amino, or any of the Z substituents; and

25

(b) a *cis/trans* isomerase capable of converting at least one of the 9-, 11-, or 13-double bonds from the trans configuration to the *cis*-configuration.

5



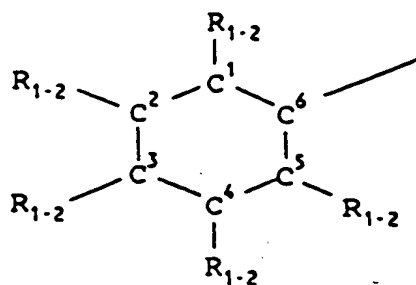
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from the corresponding all-trans configuration material,  
said method comprising contacting said all-trans  
configuration material with a *cis/trans* isomerase under  
30 isomerization conditions.

24. A method according to claim 23 wherein Ring is a cyclohexyl ring having the following structure:



10 wherein:

each R is independently selected from H, halogen, alkyl, aryl, hydroxy, thiol, alkoxy, thioalkoxy, amino, or any of the 2 substituents;

15 any one of C<sup>2</sup>, C<sup>3</sup>, or C<sup>4</sup> can be replaced with -O-, carbonyl (>CO), -S-, -S(O)-, -S(O)<sub>2</sub>-, thiocarbonyl (>CS), or -NR<sup>''</sup>-;

R<sup>''</sup> is hydrogen, alkyl, hydroxy, thiol, or alkoxy acyl; and

20 said cyclic moiety exists as the saturated, 2-ene, 3-ene, 4-ene, or 5-ene mono-unsaturated isomer, or the 2,4-, 2,5-, or 3,5-diene derivative thereof.

25. A method according to claim 23 wherein said contacting is carried out in vivo.

26. A method according to claim 25 wherein said contacting is carried out in Schneider cells.

27. A method according to claim 23 wherein said contacting is carried out in vitro.



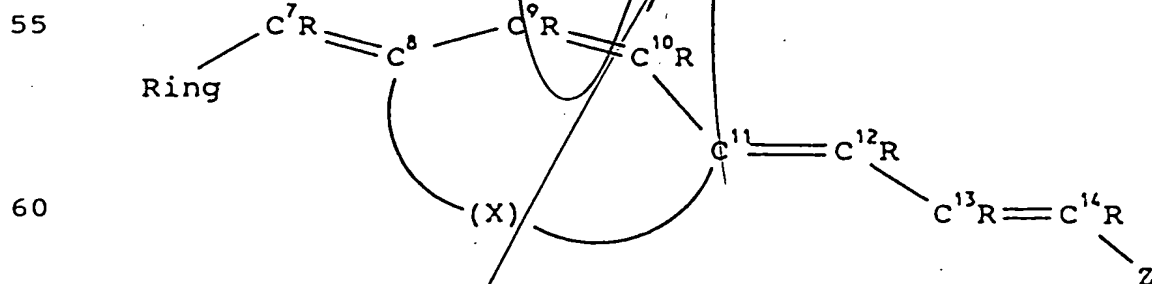
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above], thioesters of thioalkyl groups  
 $[-(CR'_2)_n-S-CS-R']$ , wherein  $R'$  and  $n$  are as defined  
 above], aminoalkyl  $[-(CR'_2)_n-NR'_2]$ , wherein  $R'$  and  
 40  $n$  are as defined above], N-acyl aminoalkyl  
 $[-(CR'_2)_n-NR'-CO-R'']$ , wherein  $R'$  and  $n$  are as  
 defined above and  $R''$  is a lower alkyl or benzyl],  
 carbamate  $[-(CR'_2)_n-NR'-CO-OR']$  or  
 $-(CR'_2)_n-O-CO-NR'_2$ , wherein  $R'$  and  $n$  are as  
 45 defined above]; and

each  $R$  is independently selected from H,  
 halogen, alkyl, aryl, hydroxy, thiol, alkoxy,  
 thioalkoxy, amino, or any of the  $Z$  substituents,  
 with the proviso that Structure A is not  
 50 9-*cis*-retinoic acid or 9,13-*dicis*-retinoic acid;  
 or

any two or more of the  $R$  groups can be  
 linked to one another to form one or more ring  
 structures;



Structure I;

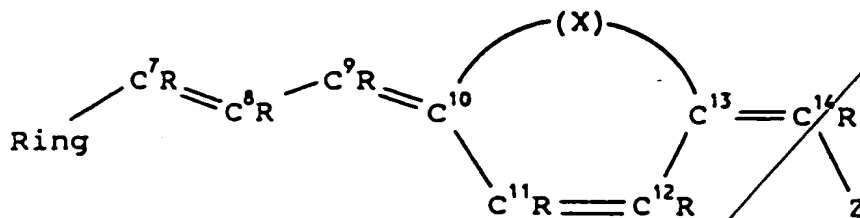
wherein:

"Ring",  $Z$  and  $R$  are as defined above;  
 65  $X$  is  $-[(CR_2)_x-X'-(CR_2)_y]-$ ,  
 $X'$  is selected from  $-O-$ , carbonyl,  $-S-$ ,  $-S(O)-$ ,  $-S(O)_2-$ ,  
 thiocarbonyl,  $-NR''-$ , or  $-CR_2-$ ,  
 $R''$  is hydrogen, alkyl, hydroxy, thiol, or alkoxy  
 acyl;  
 70  $x$  is 0, 1 or 2,  
 $y$  is 0, 1, or 2, and  
 $x + y \leq 2$ ;

**SUBSTITUTE SHEET**

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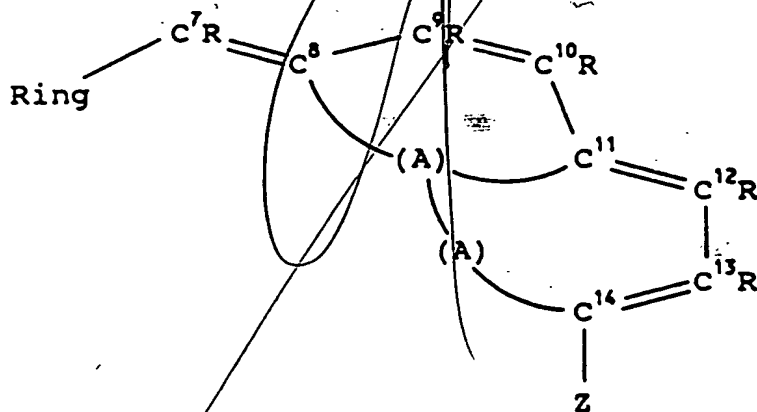
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Structure II;

wherein:

X, X', R, R'', Z, Ring, x and y are as defined above;

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Structure III

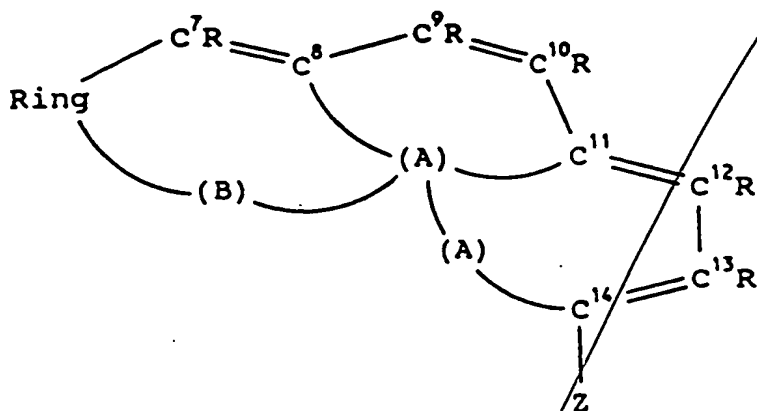
wherein:

one A is X and the other A is X', and  
X, X', R, R'', Z, Ring, x and y are as defined above;

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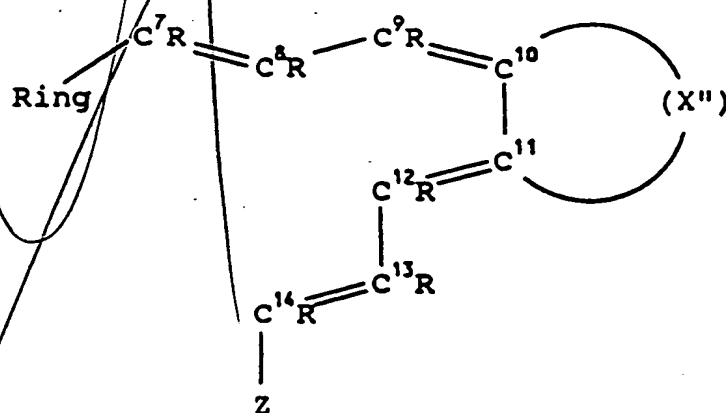
Structure IV;

wherein:

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one A is X and the other A is X',  
 B is X'', and  
 X, X', R, R'', Z, Ring, x and y are as  
 defined above;

120

Structure V;

125 wherein:

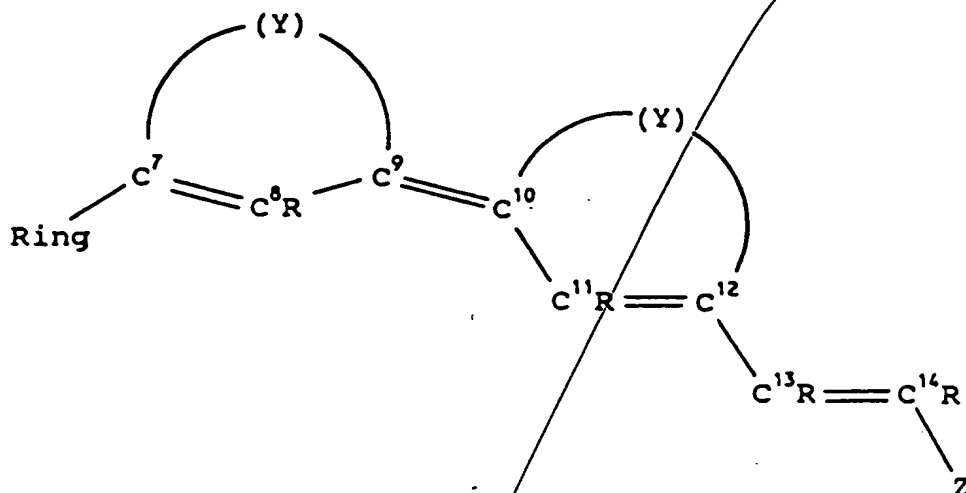
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$X''$  is  $-[(CR_2)_a-X'-(CR_2)_b]-$ ,  
 $X'$ , R, R'', Ring and Z are as defined above,  
 a is 0, 1, 2, 3 or 4,  
 b is 0, 1, 2, 3, or 4, and  
 $a + b$  is  $\geq 2$ , but  $\leq 4$ ;



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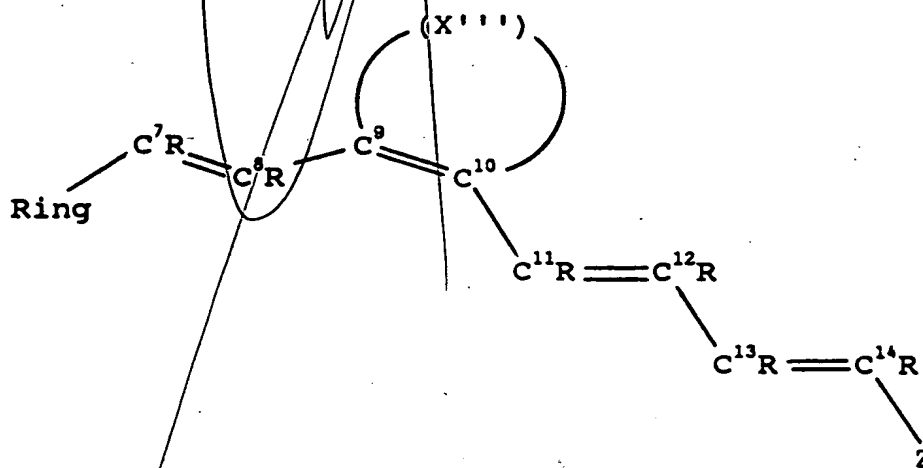
Structure VI;

wherein:

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Y is  $-(\text{CR}_2)_c-\text{X}'-(\text{CR}_2)_d-$ ,  
 $\text{X}'$ , R, R'', Ring and Z are as defined above,  
 c is 0, 1, 2 or 3,  
 d is 0, 1, 2 or 3, and  
 $c + d \geq 1$ , but  $\leq 3$ ; and

150



155

Structure VII

wherein:

160

$\text{X}'''$  is  $\text{X}''$  or an unsaturated linking group  
 having the structure:

$-[Q = CR - J]-$ ,

wherein Q is  $-N=$  or  $-CR=$ , and J is  $-CR=CR-$ ,  $-N=CR-$ ,  $-CR=N-$ ,  $-O-$ ,  $-S-$ , or  $-NR''-$ ,

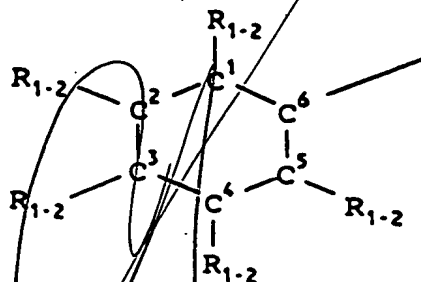
165

thereby incorporating  $C^9$  and  $C^{10}$  of the rexoid compound into an aromatic (or pseudo-aromatic) ring, and

$X'$ ,  $X''$ , R,  $R''$ , Ring, Z, a and b are as defined above.

29. A composition according to claim 28 wherein Ring is a cyclohexyl ring having the following structure:

5



10

wherein:

each R is independently selected from H, halogen, alkyl, aryl, hydroxy, thiol, alkoxy, thioalkoxy, amino, or any of the Z substituents;

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any one of  $C^2$ ,  $C^3$ , or  $C^4$  can be replaced with  $-O-$ , carbonyl ( $>CO$ ),  $-S-$ ,  $-S(O)-$ ,  $-S(O)_2-$ , thiocarbonyl ( $>CS$ ), or  $-NR''-$ ;

$R''$  is hydrogen, alkyl, hydroxy, thiol, or alkoxy acyl; and

20

said cyclic moiety exists as the saturated, 2-ene, 3-ene, 4-ene, or 5-ene mono-unsaturated isomer, or the 2,4-, 2,5-, or 3,5-diene derivative thereof; or an aromatic derivative thereof.

add  
C1

add  
C1